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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,126	03/14/2001	Torben Halkier	3631-0108P	6308

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/20/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 04/20/2007.

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mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	09/787,126	HALKIER ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,8-12,17-24,28 and 57-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,8-12,17-24,28 and 57-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060920, 20070118*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *seq. alignment*.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statement (IDS) filed 20 September 2006 and 18 January 2007 have been entered. Applicant's amendment of the claims filed 17 January 2007 is acknowledged.

Claims 2-4, 6, 7, 13-16, 25-27 and 29-56 have been cancelled. Claims 88 and 89 have been added. Claims 1, 5, 8-12, 17-24, 28 and 57-89 are pending and under examination in this office action. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Objection Withdrawn

The objection to claim 65 for typographical error is withdrawn in response to applicant's amendment of the claim.

Claim Rejections Maintained/New Grounds of Rejections

Claims 1, 5, 8-12, 17-24, 28 and 57-87 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U. S. Patent No: 6,645,500. The rejection also applies to the newly added claim 88 and 89. Applicant has not addressed the rejection.

Claims 1, 5, 8-12, 17-24, 28 are 57-89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method for in vivo down-regulation of OPGL activity or for treating excessive bone loss in a mammal, the*

method comprising administering to the mammal an immunologically effective amount of at least one modified mammalian OPGL polypeptide which has a result that immunization of the mammal with the modified OPGL polypeptide induces production of antibodies against the modified OPGL polypeptide that are cross-reactive to the mammal's own OPGL polypeptide, and down-regulates the mammals own OPGL activity, wherein said modified OPGL polypeptide comprises the sequence of SEQ ID NO: 2 or the sequence of residues 158-316 of SEQ ID NO: 2, and at least one foreign T helper epitope (T_H), does not reasonably provide enablement for other permutations of the claimed formula, substitutions, insertions, deletions, and alterations of the amino acid sequence SEQ ID NO: 2, or subsequences thereof, or analogue thereof, nor enabling for prophylactic treatment or preventing excessive bone loss. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicant argues that the present invention is focused on immunogenic or vaccine activity of modified OPGL molecules which have been modified to promote an immune response directed against the modified OPGL which is cross-reactive with the mammal's self OPGL. Applicant argues that the present specification is "presumptively" enabling and sufficient, and Examiner has not provided evidence that substantiates the rejections. As for the number of T-cell and B-cell epitopes, Applicant argues that the specification teaches that at least one T-cell epitope and at least one B-cell epitope is required in the claimed modified OPGL polypeptides. As for the length and identity of B-cell epitopes, Applicant argues that the whole OPGL sequence, or the active site of

OPGL (amino acid 158-316), or subsequences of OPGL (e.g., amino acids 171-193, 199-219, 222-247, 257-262 and 286-317 of SEQ ID NO: 2), may be used as the B-cell epitope sequence. As for the parts of OPGL that may be used to generate the immune response, Applicant argues that both active site OPGL sequences and OPGL sequences outside the active site are attractive for use, because OPGL sequences outside the active site would engage the clearing autoimmune response, but would not likely sterically block OPGL activity.

Applicant's arguments have been fully considered. As for the number of T-cell and B-cell epitopes, Applicant's arguments have been found to be persuasive. However, the rest of the arguments have not been found to be persuasive for reasons set forth in the previous office actions and for the following.

The specification has disclosed modified mammalian OPGL polypeptides comprising OPGL (SEQ ID NO: 2) or the sequence of residues 158-316 (the TNF-like domain) of SEQ ID NO: 2, and at least one foreign T helper epitope (T_H). Such a modified OPGL polypeptide when administered to a mammal, can induce production of antibodies against the modified OPGL polypeptide that are cross-reactive to the mammal's own OPGL polypeptide, and down-regulates OPGL activity in the mammal. Since OPGL activates mature osteoclasts and promotes bone resorption, immunogens capable of inducing antibodies cross-reactive with self-OPGL can be used for down-regulation of OPGL so that diseases such as osteoporosis can be treated. Applicant, however, has not provided guidance for the broad genus of modified OPGL polypeptides that can be used for *in vivo* down-regulation of OPGL. The claims read on

OPGL subsequences containing B-cell epitopes and further modified with amino acid substitutions, deletions, insertions, or additions, or any combination thereof, to the OPGL sequences. Saha et al. (BMC Genomics, 2005, 6:79) teaches that B-cell epitopes are antigenic regions recognized by the binding sites of Ig molecules, and these epitopes can be classified into two categories: i) conformational/discontinuous epitope, and ii) linear/continuous epitope (1st paragraph in Background). Saha et al. teach that one goal of designing synthetic linear peptides is to induce neutralizing antibodies against the pathogen, however, in some cases, these linear epitopes fail to produce neutralizing antibodies and do not give protective immunity (pp. 6, right column). Further, Blythe et al. (Protein Sci., 2005, 14:246-248) evaluated the existing methods for predicting the location of B-cell epitopes based on sequence profiling, and concluded that even the best set of scales and parameters performed only marginally better than random (see Abstract). Similarly, Serguei et al. (Arch. Biochem. Biophys. 2002, 398 (2):269-274) examined antigenic core epitopes using cytochrome P450cam as a template, and found that the whole set of continuous antigenic sites of P450cam covers about 45% of the P450cam sequence, however, immunodominant sites, the so called "antigenic core", represent only 9% of the protein sequence (see abstract). These references clearly teach that determining B-cell epitopes in a polypeptide that are capable of inducing neutralizing antibodies against the polypeptide is not routine and requires undue experimentation. Applicant has not provided sufficient teachings for the length and identity of B-cell epitopes for OPGL that can induce production of antibodies against a mammal's own OPGL polypeptide (autoantibodies), and down-regulate OPGL

activity in the mammal. The recitations of "a subsequence of SEQ ID NO: 2", or "an analogue of the modified OPGL polypeptide", or those modified OPGL fragments in a region of 171-193, 199-219, 22-247, 257-262 or 286-317 of SEQ ID NO: 2 with one or more amino acids alterations, read on any B-cell epitopes. For example, the specification defines "subsequence" as any consecutive stretch of at least 3 amino acids, or of at least 3 nucleotides (encoding one amino acid) derived from OPGL, and defines "analogue" as an OPGL polypeptide which has been subjected to changes in its primary structure (pp. 11, lines 11-28). It is unpredictable that these sequences or B-cell epitopes can function as an immunogen to generate autoantibodies specific to neutralize endogenous OPGL.

In addition, claims 75-87 read on prophylactic treatment or preventing excessive bone loss. Kulak et al. (Int. J. Fertil. Womens Med., 1998, 43(2):56-64) teach that prevention of excessive bone loss, e,g. osteoporosis, requires combining efforts including 1) achieving optimal peak bone mass during childhood, adolescence and early adulthood; 2) maintaining bone mass that has been acquired; and 3) counteracting the process of age-related bone loss by hormone replacement therapy (see Abstract). Applicant has not shown sufficient support that the instant modified OPGL polypeptide can provide prophylactic treatment or prevent excessive bone loss.

Thus, without detailed guidance as to the nature of the modified OPGL immunogen, and prophylactic treatment, the artisan would be unable to identify and use such molecules for *in vivo* down regulation of OPGL activity in a mammal or for treating or preventing excessive bone loss in a patient. Since the specification does not teach

the correlation of structure/function, one of skill in the art would evaluate all non-exemplified OPGL-B-cell moiety combinations and modifications for down-regulating OPGL activity *in vivo*. Thus, undue experimentation would be required for the artisan to make and use the invention as broadly claimed.

Claims 1, 5, 8-12, 17-24, 28 are 57-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues that in regard to the B-cell epitopes, Applicant discloses that the whole OPGL sequence (SEQ ID NO: 2), or the subsequences of OPGL (e.g., amino acids 171-193, 199-219, 222-247, 257-262 and 286-317 of SEQ ID NO: 2), or the active site of OPGL (amino acid 158-316), may be used as the B-cell epitope sequence.

Applicant's arguments have been fully considered but have not been found to be persuasive for reasons set forth in the previous office action and for the reasons discussed above.

As discussed above and previously, the claims are broad in that they encompass a large genus of modified OPGL polypeptides. Such genus includes the polypeptides presented in the formulas I-III, modified OPGL sequences with amino acid substitutions, deletions, insertions, or additions, or any combination thereof, modified OPGL sequences with a substitution of at least one amino acid within a position in

subsequences 171-193, 199-219, 222-247 257-262 and 286-317, subsequences of SEQ ID NO: 2, and analogue thereof. The claims are drawn to a myriad of B-cell epitopes/OPGL combinations and further modifications. There is no disclosure of complete or partial structure, physical and/or chemical properties, or methods of making the claimed product. Merely reciting "the modified OPGL polypeptide has modifications", "which are introduced between the preserved B-cell epitopes", or "at least one modification in the form of at least one foreign T helper lymphocyte epitope", does not provide sufficient written description and evidence of procession of the claimed genus. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required.

Therefore, only a modified mammalian OPGL polypeptide comprising the full-length of OPGL (SEQ ID NO: 2), or the sequence of residues 158-316 of SEQ ID NO: 2, and a foreign T helper epitope (T_H), but not the full scope of the claimed modified mammalian OPGL polypeptides, is adequately described in the disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 9-11, 20-22, 57, 59, 61-67, 69-71, 75-77, 79-81, 85, 88 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyle et al. (U. S. Patent

No: 6,316,406 B1, which has a priority filing date on 16 April 1997), in view of Jensen et al. (European Cytokine Network, 1996, Vol. 7(2), pp. 306).

The claims are drawn to a method for *in vivo* down-regulation of OPGL activity or for treating excessive bone loss in a mammal, e.g., a human being, the method comprising effecting presentation or administering to the mammal an immunologically effective amount of a modified OPGL polypeptide having a general structure as in formula I, which contains subsequences of OPGL and mutants thereof, and at least one foreign T helper lymphocyte epitope, whereby the mammals own OPGL is down-regulated due to binding to antibodies induced by immunization with the modified OPGL polypeptide, OPGL being a protein which acts as an osteoclast differentiation factor and which has the amino acid sequence of SEQ ID NO: 2 for human OPGL (claims 1, 5, 9, 57, 61-67, 69-71, 75-77, 79-81, 85, 88, 89), wherein the foreign T helper lymphocyte epitope is capable of binding to MHC class II molecules and selected from the group consisting of a natural T-cell epitope and an artificial MHC-II binding peptide sequence (claims 10, 11), wherein presentation is effected by having at least two copies of the modified OPGL polypeptide covalently or noncovalently linked to a carrier, formulated with an adjuvant, and administered via a route such as the parenteral route (claims 20, 21, 22, 59).

The '406 patent teaches a novel member of the tumor necrosis factor (TNF) family, an OPG binding protein which is identical to the OPGL of SEQ ID NO: 2 (see alignment) and is involved in the formation and activity of osteoclasts (column 2, lines 22-37). The '406 patent teaches a method for *in vivo* decreasing the activity of the OPG

binding protein comprising administering to patients suffering from bone disorders, e.g., osteoporosis, an antagonist of OPG binding protein, and such an antagonist includes antibodies, soluble forms of OPG binding protein, fragments and analogues of OPG binding protein (column 11, line 64 through column 12, line 39, column 8, lines 4-44, column 10, lines 4-8). The '406 patent teaches compositions comprising the OPG binding protein antagonists which are incorporated into carriers such as liposomes (multiple copies of an OPG binding protein antagonist noncovalently linked to a carrier), formulated with an adjuvant, and administered by injection (column 10, lines 10-57).

The '406 patent, however, does not teach that the antagonist of OPG binding protein includes a modification in which at least one foreign T-helper epitope is introduced into the polypeptide, and such modification promotes an immune response in the patient directed against the modified polypeptide and cross-reactive with the patient's self OPG binding protein.

Jensen teaches making and using TNFα analogues which contain T cell epitope, e.g., hen egg lysozyme T cell epitope (HEL81-96) or ovalbumin T cell epitope (OVA323-339) for *in vivo* down-regulation of TNFα. Jensen teaches that the immune system can be used to down-regulation proteins which may cause diseases. Jensen teaches that self-proteins are processed and presented by MHC class II molecules on the surface of APC, however, the main reason for the lack of circulating autoantibodies in the individual is the lack of strong T cell help due to induction of efficient T cell tolerance toward tolerodominant T cell epitopes in the self-antigen. Jensen teaches that by introducing foreign T cell epitope, the TNFα analogues were able to induce high-titred

autoantibodies against native murine TNFα and down-regulate its activity, and mice immunized with the TNFα analogues were less susceptible to several TNFα induced diseases. Jensen indicates that this opens a long array of novel therapeutic possibilities (see Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the '406 patent, with those of Jensen, to modify the OPG binding protein by introducing a foreign T cell epitope into the molecule. One of ordinary skill in the art would have been motivated to combine the teachings, because the '406 patent teaches that decreasing the activity of the OPG binding protein *in vivo* can be used therapeutically to treat patients suffering from bone disorders, e.g., osteoporosis, and the down-regulation of the OPG binding protein can be achieved by an OPG binding protein antagonist derived from the polypeptide, and Jensen teaches using mutant TNFα (the same family protein as OPG binding protein) which contain foreign T cell epitope to down-regulate TNFα *in vivo*, and such down-regulation is caused by inducing high-titred autoantibodies against native TNFα, and that mice immunized with the TNFα analogues were less susceptible to several TNFα induced diseases. Therefore, the combined teachings provide a reasonable expectation of successfully down-regulating OPG binding protein (OPGL) and treating diseases caused by the protein in a patient.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
April 5, 2007

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER

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US-09-052-521C-4
; Sequence 4, Application US/09052521C
; Patent No. 6316408
; GENERAL INFORMATION:
;  APPLICANT:  Boyle, William J.
;  TITLE OF INVENTION:  Osteoprotegerin Binding Proteins and Receptors
;  FILE REFERENCE:  A-451Brv
;  CURRENT APPLICATION NUMBER: US/09/052,521C
;  CURRENT FILING DATE:  1998-03-30
;  PRIOR APPLICATION NUMBER:  08/880,855
;  PRIOR FILING DATE:  1997-06-23
;  PRIOR APPLICATION NUMBER:  08/842,842
;  PRIOR FILING DATE:  1997-04-16
;  NUMBER OF SEQ ID NOS:  40
;  SOFTWARE:  PatentIn Ver. 2.1
; SEQ ID NO 4
;   LENGTH: 317
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;   ORGANISM: Human
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